93

Pharmacokinetics of TMC125 in HIV-negative Volunteers with Mild or Moderate Hepatic Impairment

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Introduction

- TMC125 (etravirine; ETR) is a next-generation NNRTI with potent activity against both wild-type HIV-1 and HIV-1 resistant to currently approved NNRTIs[1]
- Two phase III trials (DUET-1 and DUET-2) demonstrated significant antiviral benefit after 24 weeks of treatment with TMC125 in treatment-experienced patients with resistance to current NNRTIs. Except for a higher incidence of rash, patients treated with TMC125 had an adverse event (AE) profile similar to placebo[2,3]
- TMC125 is mainly eliminated via the hepatobiliary route and is predominantly metabolized by the cytochrome P450 enzymes CYP3A4, CYP2C9 and CYP2C19, followed by glucuronidation. The drug itself is an inducer of CYP3A4 and an inhibitor of CYP2C9 and 2C19 (IC_{50} = 10.5 µg/mL [24.2µM])[4]
- Antiretroviral treatment in patients with hepatic impairment may lead to enhanced liver toxicity and/or altered pharmacokinetics (PKs) of the administered drugs[5,6]
- To support administration of TMC125 in patients with hepatic impairment, a PK study in this population was conducted

Methods

- TMC125-C125 was a phase I, open-label, multiple dose PK trial in two sequential stages in HIV-negative volunteers with mild (Class A,Child-Pugh[7] score 5–6) or moderate (Class B, Child-Pugh[7] score 7–9) hepatic impairment **(Figure 1)**

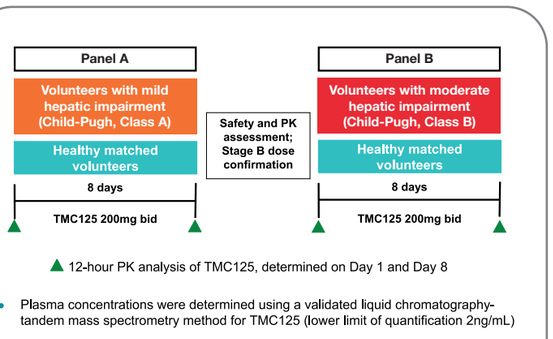

Figure 1. Study design scheme and PK analyses

- In both stages, healthy HIV-1-negative volunteers matched by age, sex, race and BMI served as controls
- Concomitant medication for the management of hepatic impairment was allowed
- All volunteers received TMC125 200mg bid (phase III/commercial formulation) for 7 days with a morning dose on Day 8
- Safety and tolerability assessments (AEs; laboratory assessments; electrocardiograms; vital signs; physical examinations) were performed throughout the trial
  - Post-treatment safety visits took place 7 days and 31 (±1) days after the last intake of trial medication
  - Severity and drug relationship of AEs to TMC125 were recorded

Table 1. Demographics

Demographic parameter, median (range) unless indicated	Panel A: Mild hepatic impairment[a] (n=8)	Panel A: Healthy (n=8)	Panel B: Moderate hepatic impairment[b] (n=8)	Panel B: Healthy (n=8)
Age, years	57 (41–65)	56 (44–66)	54 (44–64)	51 (42–63)
Male, n (%)	5 (62)	5 (62)	6 (75)	6 (75)
Caucasian, n (%)	8 (100)	8 (100)	8 (100)	8 (100)
Height, cm	171 (160–183)	172 (157–181)	174 (158–198)	175 (155–190)
Weight, kg	74 (58–101)	72 (57–89)	79 (60–125)	82 (55–96)
BMI, kg/m²	26 (20–32)	26 (23–29)	26 (22–32)	27 (23–31)

Etiology of hepatic impairment was alcoholic cirrhosis except one case of HCV cirrhosis and one case of HCV plus alcoholic cirrhosis
HCV = hepatitis C virus
[a]Child-Pugh, Class A
[b]Child-Pugh, Class B

- A non-compartmental model with extravascular input was used for PK analysis; PK and statistical analyses were performed using WinNonLin Professional™ 4.1 (Pharsight Corporation, Mountain View, CA, USA) and Microsoft Excel® (version 2000; Microsoft, Redmond, WA, USA), and SAS (version 9.1.3; SAS Institute Inc., Cary, NC, USA)
- Descriptive statistics were calculated for the PK parameters of TMC125. Least squares mean (LSM) ratios for volunteers with hepatic impairment and their matched healthy controls were estimated with a linear mixed effects model. Primary TMC125 PK parameters on Day 1 and Day 8 were:
  - C_{max} (ng/mL)
  - C_{min} (ng/mL)
  - AUC_{12h} (ng•h/mL), calculated by linear trapezoidal summation
- Safety parameters were evaluated by descriptive statistics and frequency tabulations
- The trial protocol was reviewed and approved by the appropriate institutional ethics committee and health authorities; the trial was conducted in accordance with the Declaration of Helsinki

Results

- Volunteer demographics are described in **Table 1**
- The systemic exposure to TMC125 in volunteers with mild (**Figure 2** and **Table 2**) or moderate (**Figure 3** and **Table 3**) hepatic impairment was comparable to that in healthy volunteers

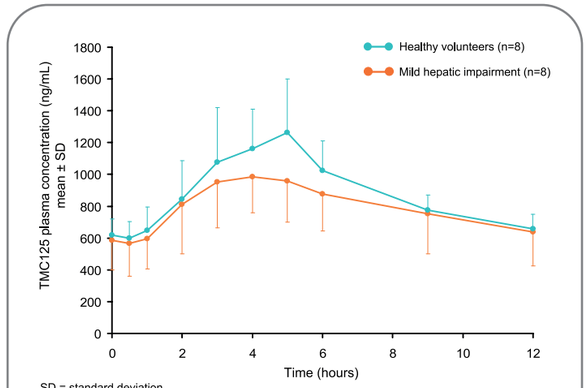

Figure 2. TMC125 plasma PK profile in volunteers with mild hepatic impairment on Day 8

Table 2. TMC125 PK parameters (mean ± SD) in volunteers with mild hepatic impairment

PK parameter		Mild hepatic impairment	Healthy	LS mean ratio (90% CI)
Day 1	C_{max} (ng/mL)	467 ± 158	499 ± 149	0.92 (0.69–1.21)
	AUC_{12h} (ng•h/mL)	2903 ± 816	2972 ± 1105	0.99 (0.75–1.29)
Day 8	C_{min} (ng/mL)	550 ± 192	594 ± 100	0.87 (0.65–1.17)
	C_{max} (ng/mL)	1060 ± 268	1339 ± 357	0.79 (0.63–1.00)
	AUC_{12h} (ng•h/mL)	9546 ± 2630	10650 ± 1688	0.87 (0.69–1.09)

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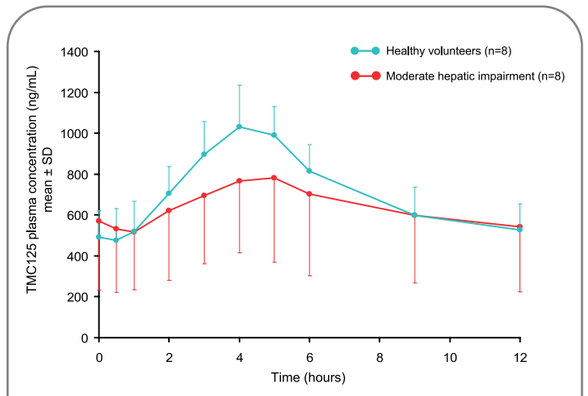

Figure 3. TMC125 plasma PK profile in volunteers with moderate hepatic impairment on Day 8

Table 3. TMC125 PK parameters (mean ± SD) in volunteers with moderate hepatic impairment

PK parameter		Moderate hepatic impairment	Healthy	LS mean ratio (90% CI)
Day 1	C_{max} (ng/mL)	268 ±101	414 ±123	0.63 (0.47–0.85)
	AUC_{12h} (ng•h/mL)	1846 ± 808	2293 ± 664	0.77 (0.55–1.08)
Day 8	C_{min} (ng/mL)	499 ± 293	462 ± 128	0.98 (0.68–1.42)
	C_{max} (ng/mL)	818 ± 394	1054 ± 194	0.72 (0.54–0.96)
	AUC_{12h} (ng•h/mL)	7665 ± 4122	8584 ± 1560	0.82 (0.60–1.11)

Safety and tolerability

- All volunteers completed the trial
- The most frequently reported AEs for volunteers with mild hepatic impairment were nausea and fatigue (each in 2 volunteers)
- Dizziness and muscle spasms were the most common AEs for volunteers with moderate hepatic impairment (each in two volunteers)
- Headache, fatigue, and nausea were reported in 6, 2, and 1 healthy volunteers, respectively (both panels combined)
- No rash was reported
- All AEs reported were mild or moderate (Grade 1 and 2) in severity
- One serious AE was reported. Tachyarrhythmia with cardiac failure was reported in one volunteer with moderate hepatic impairment and pre-existing cardiomyopathy, which occurred 36 days after the last intake of TMC125
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Conclusions

- No clinically relevant difference in TMC125 PK was observed after administration in HIV-negative volunteers with and without hepatic impairment (mild/moderate)
- Short-term administration of TMC125 in HIV-negative volunteers with and without hepatic impairment was generally safe and well tolerated
- TMC125 can be administered in patients with mild or moderate hepatic impairment without dose adjustment

References

1. Vingerhoets J, et al. *J Virol* 2005;79:12773–82.
2. Madruga JV, et al. *Lancet* 2007;370:29–38.
3. Lazzarin A, et al. *Lancet* 2007;370:39–48.
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93

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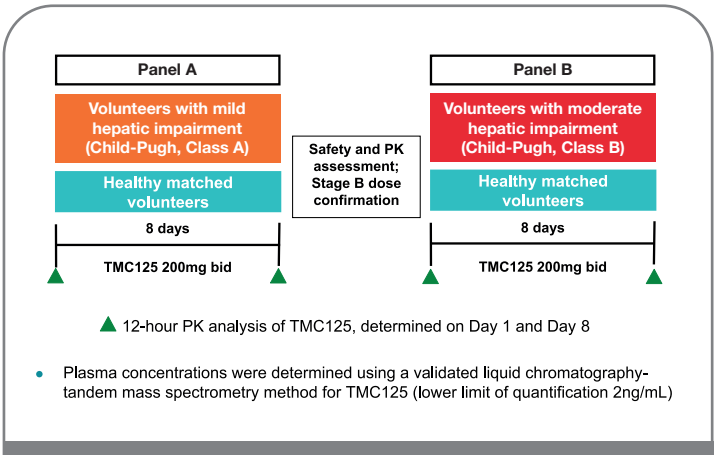

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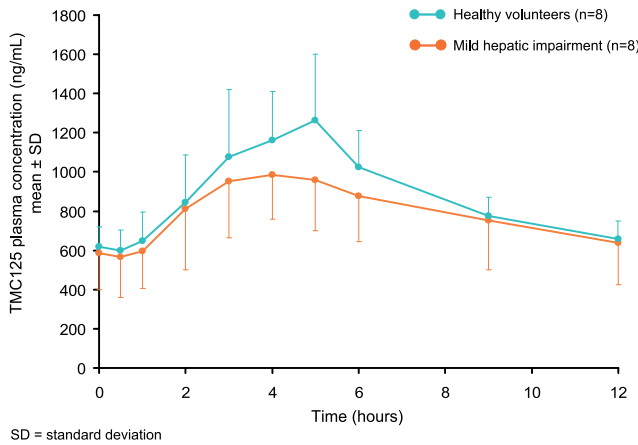

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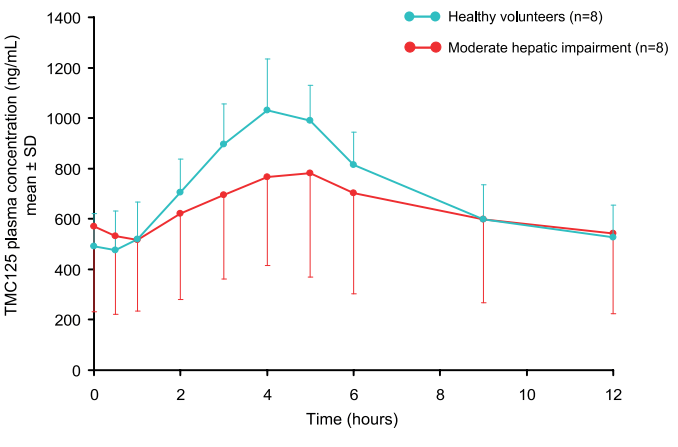

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